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Mitigation of late renal and pulmonary injury after hematopoietic stem cell transplantation

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Abstract

Purpose—To update the results of a clinical trial that assessed whether the angiotensin-converting enzyme inhibitor captopril was effective in mitigating chronic renal failure and pulmonary-related mortality in subjects undergoing total body irradiation (TBI) in preparation for hematopoietic stem cell transplantation (HSCT).

Methods and Materials—Updated records of the 55 subjects who were enrolled in this randomized controlled trial were analyzed. There were 28 on captopril and 27 on placebo. The definitions of TBI-HSCT-related chronic renal failure (and relapse) were the same as in the 2007 analysis. Pulmonary-related mortality was based on clinical or autopsy findings of pulmonary failure or infection as the primary cause of death. Follow-up data for overall and pulmonary-related mortality was supplemented by use of the National Death Index.

Results—The risk of TBI-HSCT-related chronic renal failure was lower in the captopril group (11% at 4 years) than in the placebo group (17% at 4 years) but this was not statistically significant ($p>0.2$). Analysis of mortality was greatly extended by use of the National Death Index, and no patients were lost to follow-up for reasons other than death prior to 67 months. Patient survival was higher in the captopril compared with the placebo group, but this was not statistically significant ($p>0.2$). The improvement in survival was influenced more by a decrease in pulmonary mortality (11% risk at 4 years in the captopril group vs. 26% in the placebo group, $p=0.15$) than by the decrease in chronic renal failure. There was no adverse effect on relapse risk ($p=0.4$).

Conclusions—Captopril therapy produces no detectable adverse effects when given after TBI. Captopril therapy reduces overall and pulmonary-related mortality after radiation-based HSCT and there is a trend towards mitigation of chronic renal failure.

Keywords

Radiation injury; Mitigation; Captopril; Kidney; Lung

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Introduction

Injury and failure of lungs or kidneys cause significant morbidity and mortality after HSCT (1). While multiple causes for these injuries have been identified, total body irradiation (TBI) given at the time of pre-HSCT conditioning is a major cause of injury (2,3). The chronic kidney disease that we and others have identified in these subjects is termed bone marrow transplant (BMT) nephropathy, and it is a congener of hemolytic uremic syndrome (HUS). When subjects with this syndrome have undergone kidney biopsy, the morphological appearance is of a thrombotic microangiopathy, consistent with radiation nephropathy.

Extensive pre-clinical studies have shown the benefit of angiotensin-converting-enzyme inhibitors (ACEi) for the treatment, prophylaxis and the mitigation of radiation nephropathy (4,5), and also for the prophylaxis and mitigation of radiation pneumopathy (6,7). These results led us to conduct a trial of captopril compared to placebo in subjects undergoing TBI-based HSCT at our center. This showed a favorable trend toward the benefit of captopril, for the renal endpoints and for patient survival (8), but neither were statistically significant. We have continued the longitudinal follow-up of the study subjects, and have additionally focused on their lung morbidity and mortality. Further, we have used the National Death Index to update the survival analysis (National Death Index User's Guide, National Center for Health Statistics, Centers for Disease Control and Prevention, 2009).

Methods

This is an extended analysis of a prospective single-center masked randomized placebo-controlled trial to study the effect of the ACE-inhibitor captopril on the development of kidney injury or lung death after HSCT using preparative regimens that include TBI.

The study protocol was as detailed previously (8). Study drug, captopril or placebo, was not started until marrow engraftment had occurred. This timing was based on experimental studies in which a delayed start of captopril could mitigate radiation nephropathy (9). Adults and children receiving myeloablative TBI were included. Use and doses of the study drug were as described (8).

HSCT, including preparative regimens, TBI, graft versus host disease (GVHD) prophylaxis, and supportive care was performed according to the protocols and standard institutional guidelines of the Adult and Pediatric BMT programs of the Medical College of Wisconsin. Institutional Review Board (IRB) approval has been maintained throughout this study. Chemo-irradiation conditioning was done as described in Lawton et al (10). The standard TBI dose was 14 Gy, in nine fractions equally weighted, AP/PA, over three days, using a dose rate of 8 to 20 cGy/minute and with at least four hours between fractions. Kidney shielding reduced the total kidney dose to 9.8 Gy. Lung shielding reduced the delivered lung dose to 5 to 7 Gy (11). GVHD prophylaxis used cyclosporin in almost all cases. Two patients received tacrolimus, one in each arm. Three had no calcineurin inhibitor use, two in the captopril arm, and one in the placebo arm.

If a patient in the control or captopril arm became hypertensive (three consecutive readings greater than 140/80 mmHg in adults, and greater than 120/80 in children) after HSCT, anti-hypertensive drugs could be used that were not ACE inhibitors or angiotensin II blockers. Study drug could be stopped, according to the preference of the treating physician.

If a patient became hypotensive (systolic blood pressure $\leq$ 100 mmHg) during follow-up, the study drug was withheld temporarily, and then restarted as tolerated.

For azotemia (defined as a doubling of the baseline plasma creatinine or plasma creatinine $\geq$ 2.5 mg/dl), the study drug was withheld temporarily at the discretion of the treating physician.

Records for pulmonary function tests including FEV₁ (forced expiratory volume in one second), FVC (forced vital capacity) and DLCO (diffusion capacity for carbon monoxide) were examined for the pre and post HSCT time points. The FEV₁ measures airway flow, the FVC measures lung volume, and the DLCO measures gas exchange across the alveoli. Values for patients up to 6 months before HSCT were included as pre-values if none were available immediately pre-transplant. When several post values were available, the value closest to 1 year after transplant was chosen. The range of time for post values after HSCT was 6 months to 3 years. All data are expressed as percent of reference values.

Long-term patient survival was assessed by use of hospital and clinic records, and in addition by use of the National Death Index (NDI). The latter was queried for all subjects in this study, through December 31, 2008.

Outcome Assessment

The BMT nephropathy syndrome is defined as azotemia (doubling of base-line serum creatinine or a $>50\%$ decrease in the glomerular filtration rate (GFR)), hypertension and anemia after HSCT in the absence of any other identifiable cause of kidney malfunction and in the absence of nephrotoxic drugs (2).

Stop-points for study drug included drug intolerance, the development of the BMT nephropathy syndrome (and HUS, which overlaps with BMT nephropathy) or discontinuation for any other reason by the patient or treating physician. Accrual to this study stopped in 2006. All patients were followed thereafter through November 2010 regardless of the timing or reason for discontinuation of therapy.

Pulmonary function tests (PFTs) were obtained before HSCT and at one year afterwards. Lung death was a mortality for which the primary cause was lung-related, including respiratory failure or pneumonia.

Statistics

We summarized the survival experience in the two groups using the Kaplan-Meier estimator. Relapse, death from specific causes and BMT nephropathy syndrome were summarized using the cumulative incidence function. The NDI update was used for mortality but not for the BMT nephropathy endpoint, because the NDI update did not have knowledge of the BMT nephropathy endpoint. Tests of differences in the survival rates, HUS rates, cause-specific death rates and relapse rates were carried out using the log rank test.

Endpoints of FEV₁, FVC, and DLCO at baseline between the groups and between the groups post-HSCT were compared by non-paired t-tests.

Results

Fifty-five subjects were enrolled in this study from 1998 to 2006; 52 were adults, 3 were children. All had hematologic cancers, and all were treated with chemo-irradiation conditioning before their HSCT. The average time on study drug was 2 months and did not differ for those on captopril versus those on placebo.

Follow-up had continued through 2007 in our first report; the present report is through March 2011. All subjects were identified for follow-up. There was one additional death in the captopril arm, from stroke, at 103 months. The NDI search was done in January 2011. It confirmed all deaths known by our local records. An additional eight subjects lost to follow up had no match in the NDI database and were thus assigned as being alive on December 31, 2008.

Relapse of the primary disease occurred in ten subjects of the captopril arm, and in seven of the placebo arm. The actuarial occurrence of relapse did not differ between the captopril and placebo groups ($p=0.4$)

Patient survival at eight years was 37% for the captopril arm, compared to 22% for the placebo arm, but this difference was not statistically significant ($p=0.26$) (figure 1).

A lung-related death occurred in five subjects of the placebo arm, and in two subjects of the captopril arm. The actuarial occurrence of a primary lung death was higher for subjects of the placebo arm (27%) compared to the captopril arm (11%), but this difference was not statistically significant ($p=0.15$) (figure 2).

Except DLCO values for the placebo group, pre-HSCT lung function test values fell within the normal ranges for patients of the gender, age and height. The pre-HSCT DLCO for this group was only modestly below the lower limits of normal, and was not significantly different from that of the captopril group (table 1).

Similarly, all post-HSCT values except the DLCO of the captopril group were within the normal ranges, and this value was not significantly different from that of the placebo group. Changes from pre-to post-HSCT values for all three PFT endpoints were not different in captopril or placebo groups.

The chart review using the NDI yielded one hitherto unrecognized case of BMT nephropathy. The actuarial occurrence of this primary renal endpoint is now 17% in the placebo group and 11% in the captopril group ($p>0.2$) (figure 3). For the two BMT nephropathy cases in the captopril cohort, the time on study drug was three and six days. For the rest of the captopril cohort, the median time on study drug was 71 days.

Discussion

These data extend our initial report of consistent trends for benefit of captopril to mitigate radiation injury after TBI-based HSCT. The occurrence of the BMT nephropathy syndrome or HUS is less in those subjects of the captopril arm compared to those of the placebo arm (fig 3). This positive result has occurred without increasing the relapse rate.

Patient survival is better in the captopril arm compared to the placebo arm (fig 1), and this appears to be influenced by less lung-related deaths in the captopril arm (fig 2). While neither of these differences reached statistical significance, the trend is favorable. In addition, although the present study shows only trends for benefit of captopril on the renal, pulmonary, and survival endpoints, it does show the safety of the use of captopril in irradiated patients.

The BMT nephropathy syndrome appears to be closely linked to use of TBI. Its mitigation by captopril is highly consistent with the mitigation benefit of captopril in experimental radiation nephropathy (9). The benefit of captopril in this study occurred even though the median time of use of the study drug was only two months. That is also consistent with the experimental data that use of captopril only from 3 weeks to 10 weeks after TBI exerts a

long-term mitigating benefit (5). It is possible that a longer time of use of captopril would have increased its benefit in this study, but the treating physicians had a low threshold to stop the study drug. Further, the two subjects in the captopril cohort who developed the BMT nephropathy syndrome were on study drug for less than a week. Our pre-clinical data suggest that times-on-drug of less than six weeks are ineffective. If these two subjects are re-assigned to the placebo group, the difference in the BMT nephropathy endpoint between the captopril and placebo groups becomes highly significant ($p < 0.01$ by log rank test).

The trend towards mitigation of lung-related mortality is consistent with the benefit of angiotensin-converting-enzyme (ACE) inhibitors on radiation pneumopathy in rats (7,12). The delivered mean mid lung radiation dose was less than 7 Gy in this study. At that dose, lung injury is usually held to be unlikely. Consistent with this, the pulmonary function tests were not different in the 2 groups. If anything the statistical trend was towards better preservation of DLCO in placebo rather than captopril treated subjects. Therefore, the potential pulmonary benefit does not appear to be attributable to protection of lung parenchyma by captopril.

The incidence of lung-related mortality was higher than one might have expected given that a single dose in excess of 8 Gy is generally required to produce radiation pneumonitis (13). On the other hand, in radiation accident victims who had severe hematological toxicity, but who survived >10 days and probably received < 10 Gy exposures, Flidner *et al.* reported that 72% also had pulmonary injury (14).

The subjects of our study had additional causes for lung injury, especially infection and or graft versus host disease. Those could add to the otherwise low risk of radiation injury. In that circumstance, mitigation of lung radiation injury could exert a general benefit to reduce the risk of lung-related deaths. In fact, the lung mortality benefit appears largely confined to the first 12 months after BMT, a time frame consistent with highest risks of infections as opposed to radiation associated fibrosis.

The delivered kidney radiation dose in these subjects was 9.8 Gy. In a parallel and contemporaneous cohort of subjects eligible for this study, but did not sign up for it, and who received the same renal radiation dose, cases of BMT nephropathy occurred at a rate of 10%. We estimate the equivalent single fraction dose of this regimen to be 6.5 Gy, at which one might expect some renal injury (15). Concurrent or past chemotherapy is likely to increase that risk of injury.

The long term follow up of these subjects, over four years for all subjects, has yielded no additional cases of BMT nephropathy. Luxton identified radiation nephropathy as occurring acutely, within one year, or chronically, at up to five years after irradiation (16). It is possible that longer follow-up may yield additional cases. Lesser degrees of injury could also occur, and be manifest as hypertension, without reduction in kidney function (17). We do not have follow up information for the blood pressure to confirm or disprove that possibility.

Chronic kidney disease after HSCT is common, occurring in 20% or more of long term survivors (18,19). Complete failure of kidneys leads to end-stage-renal disease(ESRD), the requirement for dialysis or transplant to sustain life; ESRD is up to sixteen times more common in subjects who have undergone HSCT, in comparison to the general population (20). Chronic kidney disease appears to have an independent adverse effect on patient survival after HSCT (21). Measures to mitigate its occurrence are thus of substantial importance.

Clinical application of our findings may be improved by identifying subjects at higher-than-average risk for radiation injury. At present, genetic markers for normal tissue radiation injury have limited value, other than for severe radiation sensitivity syndromes such as ataxia telangiectasia. It is possible that identification of biomarkers of radiation injury, such as proteinuria, could guide more focused clinical application of radiomitigators (22,23). In the HSCT patient who undergoes radiation-based pre-HSCT conditioning, angiotensin-converting-enzyme inhibitors may be useful agents to mitigate the later occurrence of chronic kidney disease.

Finally, these results further support the concept that radiation-induced normal tissue injuries can be reduced in incidence and severity by post-irradiation pharmacologic interventions and should encourage clinical trials of this approach (23).

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Fig. 1.

Actuarial patient survival according to use of captopril or placebo. There was better patient survival in the subjects of the captopril group. This survival difference did not, however, attain statistical significance ($p = 0.26$). Cases censored for survival are shown as vertical bars and the number at risk at 24 month intervals is shown in parentheses.

Fig. 2.

The cumulative incidence of pulmonary-related mortality according to use of captopril or placebo. The occurrence of pulmonary-related mortality was within the two years after the total body irradiation. The placebo group had a higher incidence than the captopril group, but this did not attain statistical significance ($p = 0.18$). Cases censored are shown as vertical bars and the number at risk at 24 month intervals is shown in parentheses; not shown are placebo cases censored for pulmonary-related mortality at 1.8, 2.2, 2.3 and 2.5 months.

Fig. 3.

The cumulative incidence of bone marrow transplant (BMT) nephropathy and hemolytic uremic syndrome (HUS) according to use of captopril or placebo. The occurrence of BMT nephropathy and HUS was within the first year after the total body irradiation. The placebo group had a higher incidence than the captopril group ($p = 0.22$). Cases censored are shown as vertical bars and the number at risk at 24 month intervals is shown in parentheses; not shown are placebo cases censored for nephropathy at 1.8, 1.9, 2.2, 2.3 and 2.7 months.

Table 1

Evolution of lung function tests for subjects of this study. Values are expressed as percent of the reference value, $\pm$ standard deviation.

FEV1	pre -HSCT	post -HSCT	delta
Placebo (n=8)	80 $\pm$ 27	90 $\pm$ 10	10.5 $\pm$ 25
Captopril (n=10)	100 $\pm$ 12.7	95.2 $\pm$ 5.1	-5.0 $\pm$ 8.4
FVC			
Placebo (n=8)	79.5 $\pm$ 27	90 $\pm$ 8.5	11 $\pm$ 22
Captopril (n=10)	97.6 $\pm$ 10.6	90.8 $\pm$ 11.8	-6.8 $\pm$ 9.1
DLCO			
Placebo (n=13)	65 $\pm$ 27.5	75 $\pm$ 19.8	2 $\pm$ 19.7
Captopril (n=14)	81 $\pm$ 17.8	66 $\pm$ 15.3	-17 $\pm$ 19.1